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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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SIEMENS CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
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EXAMINER	
REDDIG, PETER J	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,485	MUNNES ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-9,16,18 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-9,16,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Election filed June 25, 2009 in response to the Office Action of May 1, 2009 is acknowledged and has been entered. Applicant's election with traverse of Group I, claims 1, 5-10, and 16-18, in part and the species of SEQ ID NO: 4 as the additional marker and the species of determining the expression level with a hybridization based method, or with a hybridization based method utilizing arrayed probes, or with a hybridization based method utilizing individually labeled probes, or by real time real time PCR, is acknowledged.

Applicants argue that the Restriction Requirement has been traversed, because the claims of the present application relate to a single inventive concept under PCT Rule 13.1. In particular, each of the claims relates to the single inventive concept which includes determining the pattern of expression levels of SEQ ID NOS: 51, 87, 159 and 477 or kits which include primers and probes suitable for marker genes having SEQ ID NOS: 51, 87, 159 and 477. All claims directed to this concept have unity of invention. Accordingly, the Restriction Requirement is improper and should be withdrawn.

Applicants' arguments have been considered and have been found persuasive and the restriction is withdrawn.

2. Claims 1, 3, 5-9, 16, 18 and 19 are pending and under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 9 provides for the use of a predictive algorithm, but, since the claims do not set forth any steps involved in how the predictive algorithm is used, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 3, 5-9, 16, 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for *detecting, diagnosing, screening, monitoring, and/or prognosing breast carcinoma* in a subject, comprising i. determining the pattern of expression levels of at least 6, 8, 10, 15, 20, 30, or 47 *breast carcinoma* marker genes, wherein said *breast carcinoma* marker genes comprise SEQ ID NO: 51, SEQ ID NO: 87, SEQ ID NO: 159, and SEQ ID NO: 477, in a biological sample from said subject, ii. comparing the pattern of expression levels determined in (i) with one or several reference pattern(s) of expression levels, iii. *detecting, diagnosing, screening, monitoring, and/or prognosing* the state of *breast carcinoma* in said subject from the outcome of the comparison in step (ii) or a kit comprising at least 6, 8, 10, 15, 20, 30, or 47 primer pairs and probes suitable for marker genes *for breast carcinoma* comprised in a group of *breast carcinoma* marker genes comprising SEQ ID NO: 51, SEQ ID NO: 87, SEQ ID NO: 159, and SEQ ID NO: 477 and

further comprising additional *breast carcinoma* markers genes wherein the additional marker genes are listed in Table 2, *does not* reasonably provide enablement for method for characterizing the state of a neoplastic disease in a subject, comprising i. determining the pattern of expression levels of at least 6, 8, 10, 15, 20, 30, or 47 marker genes, wherein said marker genes comprise SEQ ID NO: 51, SEQ ID NO: 87, SEQ ID NO: 159, and SEQ ID NO: 477, in a biological sample from said subject, ii. comparing the pattern of expression levels determined in (i) with one or several reference pattern(s) of expression levels, iii. characterizing the state of said neoplastic disease in said subject from the outcome of the comparison in step (ii) or a kit comprising at least 6, 8, 10, 15, 20, 30, or 47 primer pairs and probes suitable for marker genes comprised in a group of marker genes comprising SEQ ID NO: 51, SEQ ID NO: 87, SEQ ID NO: 159, and SEQ ID NO: 477 and further comprising additional markers genes wherein the additional marker genes are listed in Table 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4)

the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method for characterizing the state of a neoplastic disease in a subject, comprising i. determining the pattern of expression levels of at least 6, 8, 10, 15, 20, 30, or 47 marker genes, wherein said marker genes comprise SEQ ID NO: 51, SEQ ID NO: 87, SEQ ID NO: 159, and SEQ ID NO: 477, in a biological sample from said subject, ii. comparing the pattern of expression levels determined in (i) with one or several reference pattern(s) of expression levels, iii. characterizing the state of said neoplastic disease in said subject from the outcome of the comparison in step (ii). The characterization of the neoplastic disease comprises detecting, diagnosing, screening, monitoring, and/or prognosing the neoplastic disease. Additionally, claim 19 is drawn to a kit comprising at least 6, 8, 10, 15, 20, 30, or 47 primer pairs and probes suitable for marker genes comprised in a group of marker genes comprising SEQ ID NO: 51, SEQ ID NO: 87, SEQ ID NO: 159, and SEQ ID NO: 477 and further comprising additional markers genes wherein the additional marker genes are listed in Table 2

The specification teaches that the present invention relates to the identification of 185 human genes being differentially expressed in neoplastic tissue resulting in an altered clinical behavior of a neoplastic lesion. The specification teaches that differential expression of these 185 genes is not limited to a specific neoplastic lesion in a certain tissue of the human body. See p. 2-lines 11-14. Additionally, the specification teaches that the term "marker gene," as used herein, refers to a differentially expressed gene which expression pattern may be utilized as part of predictive, prognostic or diagnostic process in malignant neoplasia or breast cancer evaluation, or which, alternatively, may be used in methods for identifying compounds useful for the

treatment or prevention of malignant neoplasia and breast cancer in particular. See p. 11-lines 15-19. Additionally, the specification teaches that "neoplastic disease" includes carcinomas and pre-malignant conditions and the specification teaches that "breast cancer" includes carcinomas and pre-malignant conditions. See p. 2-lines 18-21 and p.11-line 24 to p. 12-line 3. Thus the claims are broadly drawn to detecting, diagnosing, screening, monitoring, and/or prognosing any neoplastic disease or pre-malignant condition by detecting the expression of the claimed marker genes and marker genes that can be used for characterizing any neoplastic disease or pre-malignant condition.

The specification teaches that the invention comprises diagnosing, staging, prognosis, monitoring and therapy of breast cancer, but is not limited to breast cancer. See page 2-lines 15-20. The specification provides general methods of analyzing gene expression such as quantitative RT-PCR and expression profiling using microarrays. See Examples 1 and 2. The specification teaches methods of data analysis for gene profiling experiments. See Example 3. The specification teaches the Support Vector Machine and additional statistical test for data analysis and prediction of response. See Examples 4 -6

The specification teaches that SEQ ID NOs: 51, 87, 159 and 4 are differentially expressed in responders compared non-responders or normal healthy tissue. See Table 1A. The specification teaches that SEQ ID NO: 477 is differentially expressed in non-responding tumors compared to tumors with at least a minor therapy associated regression or normal healthy tissue. See Table 1b. It is not clear from the tables which tumor type these in which these genes were differentially expressed in, although it appears to be breast cancer. See p. 14- lines 19 and 20.

With regard to breast cancer (which is commonly understood to encompass malignant carcinomas, not pre-malignant conditions, see, Taber's Cyclopedic Medical Dictionary (1985, F.A. Davis Company, Philadelphia, p. 274)) and the claimed marker genes, Bardou et al. (J. Clin. Oncl. 2003, 21: 1973-1979) teach that the estrogen receptor (SEQ ID NO: 51) has been used since the mid-1970's as a prognostic factor for early recurrence of breast cancer. See p. 1973, 1st col. Alba et al. (Virchow Arch, 2001: 439: 435) teach that p53 (SEQ ID NO: 87) the estrogen receptor (SEQ ID NO: 51) are good prognostic markers in breast cancer metastasis. Aranda et al. (Virchow Arch, 2001: 439: 435-436) teach that p53 overexpression showed tendency to present worse prognosis. US Pat. App. Pub. 2004/0029114 A1 (Mack et al. Jan. 24, 2001) teaches that estrogen receptor 1, tumor protein p53, matrix metalloproteinase 1, and microtubule associated protein tau which are SEQ ID NOs: 51, 87, 159 and 477, respectively, as being up-regulated in breast tissue compared to normal breast tissue. See Table 4, 9, and 10 of 2004/0029114 and Tables 1a 1b, 4a, and 4b of the instant specification. US Pat. App. Pub. 2004/0029114 A1 teaches that the expression of RAB31, which is a gene in Table 2 of the instant specification, is up-regulated in breast tumor tissue compared normal breast tissue. See Table 5 and 7. US Pat. App. Pub. 2004/0029114 A1 teaches using these genes for the diagnosis and prognosis of breast cancer. See 0002, 0009, 0055, 0115, and 0221. US Pat. App. Pub. 2003/0224374 A1 Dai et al. June 18, 2001) teaches comparing the expression of the estrogen receptor 1/NM_00125, tumor protein p53, matrix metalloproteinase 1/NM_002421, and NM_00226, which are SEQ ID NOs: 51, 87, 159, and 4 respectively, for the prognosis and diagnosis of breast cancer. See Table 1, para. 0003, 0006, 0012, 0013, 0020, and 0021 of 2003/0224374 and Tables 1a 1b, 4a, and 4b of the instant specification.

Thus, the art teaches that SEQ ID NO: 47, 87, 159, and 477 are important in breast cancer/carcinoma diagnosis and prognosis. However, the claims are not limited to breast cancer and one of skill in the art cannot predictably extrapolate the teachings of the specification to the enablement of the claims because one cannot predictably extrapolate the findings in breast cancer to any neoplastic disease because of the heterogeneous nature of cancer phenotypes and their response to treatment and breast cancer is not a pre-malignant condition. In particular, as drawn to cancer heterogeneity, cancers comprise a broad group of malignant neoplasms divided into two categories, carcinoma and sarcoma. The carcinomas originate in epithelial tissues while sarcomas develop from connective tissues, see Taber's Cyclopedic Medical Dictionary (1985, F.A. Davis Company, Philadelphia, p. 274). Given that not all cancers originate from the same tissue types, it is known that cancers originate from different tissue types have different structures as well as etiologies and would present differently. Thus, it would not be predictably expected that a nexus, for example drawn to a connection between SEQ ID NOs: 51, 87, 159 and 477 and breast cancer, would be established between two cancer types that arose from different tissue types. Further, it is well known that even two carcinomas that present on the same organ have significant differences in etiology and genetic constitution. For example, Busken, C et al. (Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No: 850), teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Additionally, Kaiser (Science, 2006, 313: 1370) teaches that in a genomic analysis of mutations in breast and colon cancers, it was found that the cancer genes differ

between each colon and breast cancers and each tumor had a different pattern of mutations. Kaiser teaches that the steps to cancer may be more complex than had been anticipated, see 3rd col. Furthermore Krontiris and Capizzi (Internal Medicine, 4th Edition, Editor-in-chief Jay Stein, Elsevier Science, 1994 Chapters 71-72, pages 699-729) teach that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocols. Chemotherapeutic agents are frequently useful against a specific type of neoplasm and especially with the unpredictability of the art there are no drugs broadly effective against all forms of cancer; see Carter, S. K. et al. (Chemotherapy of Cancer; Second edition; John Wiley & Sons: New York, 1981; appendix C). Given the above, in the absence of further guidance or direction that the claimed markers can be used for characterizing any neoplastic disease, pre-malignant or malignant, other than breast carcinomas, it is clear that it is not possible to predictably extrapolate a correlation between SEQ ID NOs: 51, 87, 159 and 477 and breast carcinomas and any neoplastic disease based on the information in the specification and known in the art without undue experimentation.

The specification provides insufficient guidance with regard to these issues and provides insufficient working examples which would provide guidance to one skilled in the art and insufficient evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

5. Claims 1, 3, 5-9, 16, 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The limitations of "at least 6, 8, 10, 15, 20, 30, or 47 marker, wherein said marker comprise SEQ ID NO: 51, SEQ ID NO: 87, SEQ ID NO: 159, and SEQ ID NO: 477" in claims 1, 3, 5-9, 16, and 18 and "A kit comprising at least 6, 8, 10, 15, 20, 30, or 47 primer pairs and probes suitable for marker genes comprised in a group of marker genes comprising SEQ ID NO: 51, SEQ ID NO: 87, SEQ ID NO: 159, and SEQ ID NO: 477 and further comprising additional markers genes wherein the additional marker genes are listed in Table 2" in claim 19 have no clear support in the specification and the claims as originally filed.

A review of the specification discloses support for determining the pattern of expression levels of at least 6, 8, 10, 15, 20, 30, 47 or 67 marker genes, comprised in a group of marker genes consisting of SEQ ID NO: 1 to 165 and 472 to 491 (original claims 3), marker genes are comprised in a group of marker genes listed in Table 2 (original claim 16) and a kit comprising at least 6, 8, 10, 15, 20, 30, 47, or 67 primer pairs and probes suitable for marker genes comprised in a group of marker genes consisting of (i) SEQ ID NO: 1 to SEQ ID NO:165, and/or (ii) SEQ ID NO:472 to SEQ ID NO:491, or (iii) the marker genes listed in Table 2 (original claim 20). However, the currently claimed genera of claims 1, 3, 5-9, 16, 18 and 19 are distinct, broader genera in that they are not limited to being comprised by a group of marker genes **consisting** of SEQ ID NO: 1 to 165 and 472 to 491, the group of marker genes listed in Table 2, or the group of marker genes **consisting** of (i) SEQ ID NO: 1 to SEQ ID NO:165, and/or (ii) SEQ ID NO:472 to SEQ ID NO:491, or (iii) the marker genes listed in Table 2. Thus,

the subject matter claimed in claims 1, 3, 5-9, 16, 18 and 19 broadens the scope of the invention as originally disclosed in the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1, 3, 5-8, 16, 18 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by WO/2002/059377 (Mack et al. August 1, 2002).

WO/2002/059377 teaches detecting at least 6 marker genes comprising estrogen receptor 1, tumor protein p53, matrix metalloproteinase 1, and microtubule associated protein tau which are SEQ ID NOs: 51, 87, 159 and 477, respectively, as being up-regulated in breast tissue compared to normal breast tissue. See Table 4, 9, and 10-pages 4, 5, 114, 192, 194, 195 and 201 of WO/2002/059377 and Tables 1a 1b, 4a, and 4b of the instant specification. WO/2002/059377 and teaches detecting the expression of RAB31, which is a gene in Table 2, is up-regulated in breast tumor tissue compared normal breast tissue. See Table 4- page 115, Table 5-page 141 and 7-page152. WO/2002/059377 teaches detecting these genes for the diagnosis and prognosis of breast cancer. See page 1-lines 14-18, page 4-lines 3-7, page 9-lines 25-28, page 31-lines 1-15, and para. bridging p. 61 and 62. WO/2002/059377 teaches monitoring the efficacy of a

therapeutic treatment of breast cancer using the sequences of the invention and different times with screening assays. See p. 5- lines 1-20, p. 7-line 24 to page 8-line 8, page 62-line 18 to page 64-line 18. WO/2002/059377 teaches using the methods to evaluate treatment to determine if a treatment down regulates tumor growth or recurrence and that the molecular profiling of the invention can be used to diagnose, prognosis, or predictions based on the findings. See para. p. 5-lines 1-20, p.28, and p 61-line 29 to page 62-line 15. Thus, the broadly claimed estimation of the likelihood of success of a given mode of treatment and assessment of whether or not the subject is expected to respond to a given mode of treatment are anticipated by the methods of monitoring the efficacy of a therapeutic treatment, predicting and prognosis of WO/2002/059377 as these methods would inherently be comprised by the broadly claimed steps of estimation and assessment of claims 6 and 7. US Pat. App. Pub. 2004/0029114 teaches using predictive algorithms. See page 11-line 22 to page 13- line 30 and Table 25-page 347. WO/2002/059377 teaches kits with primers and probes for detecting the markers of the invention. See page 92-line 16 to page 93-line12 and p. 52-lines18-26.

7. Claims 1, 3, 5-8, 16, 18 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat. App. Pub. 2004/0029114 A1 (Mack et al. Jan. 24, 2001).

US Pat. App. Pub. 2004/0029114 A1 teaches detecting at least 6 marker genes comprising estrogen receptor 1, tumor protein p53, matrix metalloproteinase 1, and microtubule associated protein tau which are SEQ ID NOs: 51, 87, 159 and 477, respectively, as being up-regulated in breast tissue compared to normal breast tissue. See paragraphs 0009-0023, Table 4, 9, and 10 pages 49, 120, 121, 122 and 127 and Tables 1a 1b, 4a, and 4b of the instant specification. US Pat. App. Pub. 2004/0029114 A1 teaches detecting the expression of RAB31 is

up-regulated in breast tumor tissue compared normal breast tissue. See Table 4 page 50 and Table 5-page 75. US Pat. App. Pub. 2004/0029114 A1 teaches using these methods for the diagnosis and prognosis of breast cancer. See 0002, 0009, 0055, 0115, and 0221. US Pat. App. Pub. 2004/0029114 A1 teaches monitoring the efficacy of a therapeutic treatment of breast cancer using the sequences of the invention and different times with screening assays. See para. 0021-0023, 0044-0047, 0224-0231. US Pat. App. Pub. 2004/0029114 A1 teaches using the methods to evaluate treatment to determine if a treatment down regulates tumor growth or recurrence and that the molecular profiling of the invention can be used to diagnose, prognosis, or predictions based on the findings. See para. 0021-0023, 0106, 0221 and 0222. Thus, the broadly claimed estimation of the likelihood of success of a given mode of treatment and assessment of whether or not the subject is expected to respond to a given mode of treatment are anticipated by the methods of monitoring the efficacy of a therapeutic treatment, predicting and prognosis of US Pat. App. Pub. 2004/0029114 as these methods would inherently be comprised by the broadly claimed steps of estimation and assessment of claims 6 and 7. US Pat. App. Pub. 2004/0029114 teaches using predictive algorithms. See para. 0062-066 and Table 25-page 246. US Pat. App. Pub. 2004/0029114 teaches kits with primers and probes for the markers of the invention. See para. 0346-0348 and 0193.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 9 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO/2002/059377 (Mack et al. August 1, 2002) as applied to claim 1, 3, 5-8, 16, 18 and 19 above, and further in view of US Pat. App. Pub. 2003/0224374 A1 (Dai et al. June 18, 2001), in view of US Pat App. Pub. 2003/0198972 (Erlander et al. Dec. 21, 2001), and in view of US Pat. App. Pub. 2004/0002067 A1 (Erlander et al. Dec. 21, 2001).

It is noted that claim 16 for the instant rejection is alternatively being examined as drawn to the elected species SEQ ID NO: 4 from Table 2.

WO/2002/059377 teaches as set forth above, but does not teach determining the expression of SEQ ID NO: 4 from Table 2 or using a Support Vector Machine predictive algorithm.

US Pat. App. Pub. 2003/0224374 A1 teaches comparing the expression at least 6 marker genes comprising the estrogen receptor 1/NM_00125, tumor protein p53, matrix metalloproteinase 1/NM_002421, and NM_00226, which are SEQ ID NOs: 51, 87, 159, and 4 respectively, for the prognosis and diagnosis of breast cancer. See Table 1, para. 0003, 0006, 0012, 0013, 0020, and 0021 and Tables 1a 1b, 4a, and 4b of the instant specification.

US Pat App. Pub. 2003/0198972 teaches that karyopherin alpha 2 (KPNA2, RAG cohort 1, importin alpha), which is SEQ ID NO: 4 is increased in Grade III breast cancer samples. See Abstract, para.0107, Table 6 and 9 and 2 of the instant specification.

US Pat. App. Pub. 2004/002067 teaches using a support vector machine (SVM) for analysis of micoarray data and diagnostic tests. US Pat. App. Pub. 2004/002067 teaches:

> SVMs are considered a supervised computer learning method because they exploit prior knowledge of gene function to identify unknown genes of similar function from expression data. SVMs avoid several problems associated with unsupervised clustering methods, such as hierarchical clustering and self-organizing maps.") Other algorithms, such as, but not limited to, linear discriminate analysis, logistic regression, cluster analysis, K-th nearest neighbor, or neural nets.

See para.0096-0099

It would have been *prima facie* obvious at the time the invention was made and one of skill in the art would have been motivated to further examine the expression of karyopherin alpha 2 (KPNA2, RAG cohort 1, importin alpha), which is SEQ ID NO: 4, in combination with the breast cancer markers examined by WO/2002/059377 for the diagnosis and characterization of breast cancer because KPNA2/SEQ ID NO: 4 had been independently identified by US Pat.

App. Pub. 2003/0224374 A1 and US Pat App. Pub. 2003/0198972 as being involved in breast cancer development and being a marker thereof. Thus, one of skill in the art would have been motivated to examine the expression of KPNA2/SEQ ID NO: 4 to confirm and validate the results found with other breast cancer markers and increase the significance of the test. Given that the methods of determining the expression of these genes were well known in the art, one of skill in the art would have had a reasonable expectation of success of performing the claimed methods.

Additionally, it would have been *prima facie* obvious at the time the invention was made and one of skill in the art would have been motivated to use a support vector machine predictive algorithm in the diagnostic and prognostic methods of WO/2002/059377 because WO/2002/059377 teaches the advantages of using this a support vector machine predictive algorithm versus other algorithms in the art. Additionally, given that the support vector machine predictive algorithm was routinely used in the art one of skill in the art would have a reasonable expectation of success in using this algorithm.

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PETER J. REDDIG whose telephone number is (571)272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Helms Larry can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Peter J Reddig/
Examiner, Art Unit 1642